Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v29i04.4374

Investigating the Drug Potential of a Natural COX Inhibitor: ADME and *In Silico* Analysis

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ABSTRACT
An essential part of the inflammatory process was played by COX-2, a crucial enzyme that catalyzed the rate-limiting stages in the conversion of arachidonic acid to prostaglandins. As opposed to other family members, COX-2 was significantly inducible during the acute inflammatory response of human bodies to wounds or infections and scarcely detectable under normal physiological conditions. As a result, the therapeutic use of selective COX-2 inhibitors has long been recognized as a successful strategy for the treatment of inflammation with few adverse effects. NSAIDs, both older and more recent, are now the most often recommended drugs for the COX-2-targeted treatment of inflammatory disorders. Natural phenols, flavonoids, stilbenes, terpenoids, quinones, and alkaloids were the primary divisions of the natural COX-2 inhibitors based on structural characteristics. A few dietary COX-2 inhibitors of natural origins also showed chemo preventive benefits by focusing on COX-2-mediated carcinogenesis in addition to their anti-inflammatory effects. It was also explored how these natural treatments may be used in the future to prevent cancer. Overall, the analysis of the COX-2 inhibitors from natural sources that have been defined open the way for the future creation of stronger and more focused COX-2 inhibitors.

KEYWORDS: COX -1/COX-2, SWISS ADME, PROTOX II.

INTRODUCTION
There are numerous powerful medicines made from natural substances that are sold on the market. The cyclooxygenase-2 (COX-2) enzyme is over expressed in a number of physical conditions, such as inflammations linked to cancer or cardiovascular ailments. Numerous active substances produced from plants have been shown to have COX-2 inhibitory action in the literature. These include xanthines, cinnamates, stilbenes, flavonoids, alkaloids, and coumarins.[1] The synthesis of prostaglandins H2, a precursor for the biosynthesis of prostacyclins, prostaglandins, and thromboxane, is catalysed by cyclooxygenases (COXs), which impact a wide range of biological functions, including the control of immunological function, preservation of renal blood flow, reproductive biology, and gastrointestinal integrity [2]. Multiple COX isoforms, each with a unique physiological expression and function, have been shown to exist in studies [3]. Two primary COX-1 isoforms, sometimes known as the "housekeeping" enzyme, control a variety of physiological reactions, including platelet aggregation and stomach cytoprotection. COX-2, on the other hand, is an inducible enzyme that is expressed in cells that mediate inflammation, such as synoviocytes,

macrophages, and monocytes, and it helps to synthesise the prostanoids that are implicated in both acute and chronic inflammatory diseases.[1]

The primary inflammatory mediators responsible for the pathophysiology of a number of diseases, including cardiovascular disease and arthritis, are prostaglandins [8]. Arachidonic acid is transformed by the endogenous cyclooxygenase (COX) enzyme into prostaglandins and thromboxanes, which produce pain, inflammation, and hyperthermia [9-11]. COX-1 and COX-2 are the two stable isoforms of this enzyme. Although the same sort of metabolic conversion is catalysed by both isoforms, the expression patterns of the two are distinct [12].Rofecoxib and celecoxib are the two selective COX-2 blockers that are used the most frequently and are accessible by prescription in the United States, Bangladesh, and India [13,14]. Although "coxib" medications are more effective, there are suggestions that long-term usage of these medications may raise your risk of heart attacks and strokes. Rofecoxib and valdecoxib are no longer available on the market as a result, as of 2004 and 2005, respectively [15-16]. Therefore, one of the most important research areas nowadays is the development of new drugs with fewer adverse effects. Finding new molecular targets that might open the door for new anti-inflammatory medications is a laborious but necessary effort being made to achieve this goal.

Flavonoids are a class of naturally occurring polyphenols that are widely present in a variety of foods and drinks made from plants. These substances have a wide range of medicinal and bioactive qualities [4-6]. Prostaglandins (PGs), which are commonly responsible for inflammation and discomfort when overexpressed, are produced in large quantities by the important enzyme COX-2. Inhibitors of COX-2 function by preventing the synthesis of PGs, fatty acid derivatives well-known for their ability to cure arthritis by reducing inflammation [7].

In order to create new antibiotics targeting both well-known and undiscovered targets, computer-aided drug design (CADD) can be used in conjunction with wet-lab approaches to understand the mechanism of drug resistance. On the other hand, a lot of repurposed medications have already received FDA approval and will thus go to the clinic for less money and sooner. A significant amount of CADD-based techniques may provide an atomic level structure-activity relationship (SAR) that is utilised to speed up the drug design process while lowering costs and time. However, many repurposed medications have already received FDA approval and will consequently go to the clinic more quickly and at a lower cost [17-20]. Recent years have seen a rise in the use of natural products from a variety of chemical families, including phenolics, quinones, The COX-inhibiting effects of flavonoids, stilbenes, terpenoids, and alkaloids [21-22,17] are quite potent . Due to their structural core scaffolds, phytoconstituents of natural origin have an advantage over their synthetic equivalents in terms of environmental compatibility, better biodegradability, and eco-friendliness, as well as improved biological functions [23].

Secondary plant metabolites called polyphenols are essential for shielding plants from UV rays and pathogen assaults [24]. They are naturally occurring substances found in a variety of foods, such as cereals, fruits, vegetables, and drinks. Grapes, apples, pears, cherries, and berries contain up to 200–300 mg of polyphenols per 100 g of fresh weight. They are also widely distributed in the goods made from these fruits. A glass of red wine, a cup of tea, or a cup of coffee has about 100 mg of polyphenols. In addition to chocolate, dry beans and grains also contain polyphenols.[25,26] The possible health advantages of dietary plant polyphenols as antioxidants have received a lot of attention in the past 10 years. Consuming diets high in plant polyphenols over the long term is protective against cancer, cardiovascular disease, diabetes, osteoporosis, and neurological illnesses, according to epidemiological study and associated meta-analysis [27,28]. Polyphenols can aid with a variety of food-related issues, including bitterness, astringency, colour, taste, odour, and oxidative stability. Numerous health advantages of plant polyphenols in the diet.

The COX-2 enzyme is similar to the COX-1 enzyme with the exception of the three amino acids that were replaced, which caused the polar hydrophilic side pocket of the COX-2 active site to be larger than the COX-1 active site. As a result, large molecules were unable to fit into the COX-1 active site but could still bind to the COX-2 enzyme.[29,30] There are three cavities (aromatic area (cavity A), aliphatic region (cavity B), and selective region) in the COX-2 active site, which is made up of 22

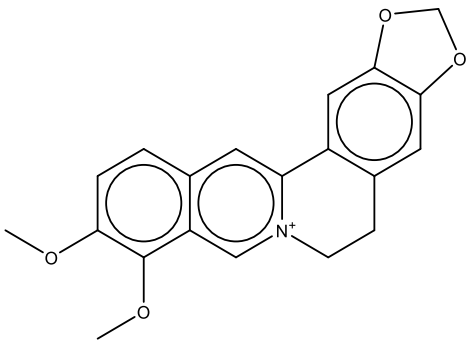
amino acids (cavity C). Specifically targeting COX-2 is a stunning illustration of heterocycle bioisostericbehaviour. pyrimidines, pyrazines, and Good bioisosteres of each other exist between isoxazolines.[31] Nabumetone1) [4-(6-methoxy-2-naphthalenyl)-2-butanone] is a nonacidic compound. Broad-spectrum antipyretic, anti-inflammatory a painkiller. Later, this medication was authorised for Bencard, Fujisawa, Ambelette and Uriach. This activity exceeds that of equivalent to indomethacin, naproxen, and aspirin.[32] 6-methoxy-2-naphthylacetic acid, an active metabolite of nabumetone Acid (6MNA) (2) is in charge of the therapeutic outcome. Nabumetone is a subpar COX-2 inhibitor with lower nephrotoxicity, instead of indomethacin.[33]

MATERIAL AND METHOD

There is vast field of natural cox inhibitor which include alkaloids, flavonoids, quinones, stilbenes and terpenoids. In this reaserch article we discuss aboutinsilico studies and ADME of some natural cox inhibitor.

1. **Alkaloids**- Isoquinoline alkaloids, which are present in nature, are excellent COX enzyme inhibitors for the prevention of many malignancies. We'll talk about a handful of them here, including berberine (1), sanguinarine (2), cavidine (3), and pseudocoptisine (4)

I. **Berberine**- Plants belonging to the genera Berberis and Coptis contain berberine (1). In both Chinese and Ayurvedic medicine, it has been utilised extensively. Berberine's anticancer effects have been examined in the past, highlighting its several cancer-fighting pathways [34,35]. Effective COX-2 transcriptional activity inhibition is possible in colon cancer cells. At doses greater than 0.3 M, it is a good inhibitor [36]. Both in vivo and in vitro studies on the effects of berberine in male Wistar rats and oral cancer cell lines (OC2) have been conducted. A 12-hour berberine treatment of OC2 decreased prostaglandin (PGE2) synthesis in a dose-dependent manner. In the carrageenan-induced air pouch in rats, berberine reduced exudate and PGE2 production [37].Berberine inhibited COX-2, which led to the death of human oral epidermal carcinoma KB cells when it was applied. Berberine reduced Mcl-1 expression and Akt phosphorylation, which in turn reduced PGE2 levels. It was determined that additional research is necessary to fully understand the anti-tumor potential of berberine [38]. By inhibiting the transcription factor nuclear factor-B (NF-B) and downregulating COX-2, berberine also has anti-inflammatory, anticancer, and proapoptotic effects [39].

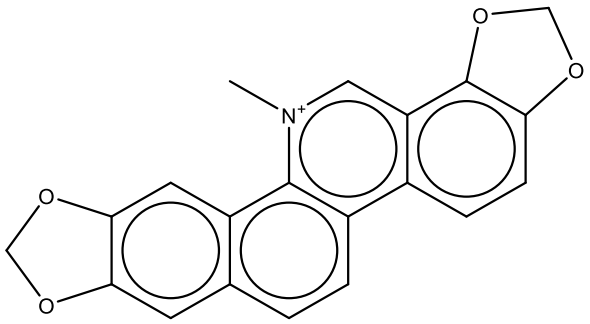


BERBERINE

II. **Sanguinarine**- Sanguinariacanadensis L. and Chelidoniummajus L. are members of the Papaveracea family, which also includes the benzophenanthridine alkaloid sanguinarine[40,41]. It is used to manage schistosomiasis and possesses antibacterial, antifungal, antitischistosomal, antiplatelet, and antiinflammatory effects [42-44].

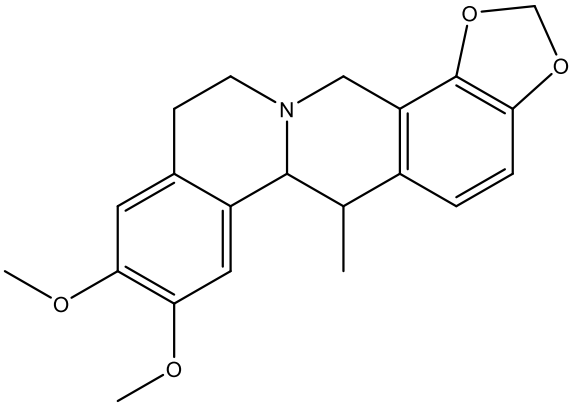
Sanguinarine is presently being studied by academics due to its possible anticancer properties [101–104]. According to data from in vitro experiments, this alkaloid often exhibits anticancer effects at doses lower than ten micromoles. Numerous cancer cells are affected by sanguinarine, which causes cell cycle arrest at various stages or apoptosis[45-52]. It significantly makes breast cancer cells more

susceptible to ligand-mediated apoptosis that is connected to tumour necrosis factor (TNF) [53]. Additionally, sanguinarine (5 mg/kg) inhibits angiogenesis in mice, has anti-invasive properties, and reverses the P-gp-mediated MDR phenotype [108-110]. For the treatment of prostate cancer, a method including the coadministration of COX-2 inhibitors and sanguinarine has been suggested [54]. The possibility of using sanguinarine as a treatment for ailments brought on by UV exposure, such as skin cancer, has also been raised [55].



SANGUINARINE

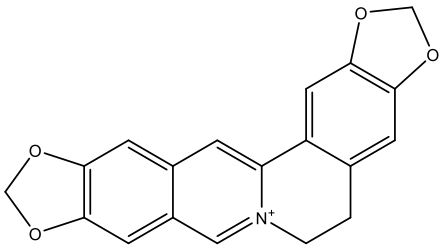
III. **Cavidine-**Cavidine was isolated from *Corydalis impatiens*. The plant has been used traditionally for the treatment of hepatitis, scabies, skin injuries, and cholecystitis in Tibetan herbal system. Niu*et al*. investigated its anti-inflammatory effects along with the mechanisms *in vitro* and *in vivo*. They used male and female Kunming mice for *in vivo* studies and LPSinduced murine peritoneal macrophages for *in vitro* studies. They used different edema models including formaldehyde induced paw edema, xylene-induced ear edema, NO-induced edema, and acetic acid-induced peritonitis in the above mentioned rats. Cavidine showed very promising results in reducing inflammation. It significantly inhibited LPS-induced TNF-α, NO production in peritoneal macrophages, and more prominently, it inhibited COX-2 selectively, thus showingpromising anti-inflammatory activity [59]



CAVIDINE

IV. **Pseudocoptisine -** Pseudocoptisine (104) is a benzylisoquinoline alkaloid that was discovered in the tubers of Corydalis turtschaninovii. It inhibits the synthesis of NO and PGE2, as well as the mRNA levels of iNOS, COX-2, TNF-a, and IL-6, in a dose-dependent manner. Additional research revealed that it suppressed ERK and p38 phosphorylation, inhibiting NF-kB activation, to lower levels of pro-inflammatory cytokines, demonstrating the potential antiinflammatory effect [56]. Corydalis bungeanaTurcz Officially, (Papaveraceae) has anti-inflammatory properties. medication found in the Chinese Pharmacopeia. Hexahydrobenzophenanthridine tetracyclic alkaloids (HAs)

Benzophenanthridine skeleton is a typical component of this plant. Corygaline A (105), corycaline A-E, and compounds 111–114 are HAs isolated from Corydalis bungeanaTurcz and their restraint of LPS-induced Evaluation of NO generation in RAW264.7 cells. The Results showed that all compounds except for 107 (IC50 14 33.8 mM) and 112 (IC50 = 23.1 mM) showed notable inhibitory effects. against NO generation, with IC50 values in the range of 1.0e2.9 mM comparable to Minocycline (31.3 mM) [57,58].



PSEUDOCOPTISINE

2. FLAVANOIDS

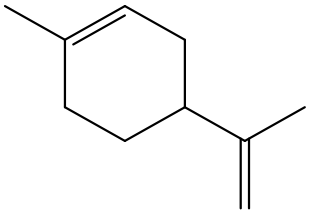
The biological/pharmacological properties of flavonoids, commonly referred to as nature's gentle medications, include anticancer, antibacterial, antiviral, antiinflammatory, immunomodulatory, and antithrombotic actions (1). The ability of flavonoids to reduce inflammation is one of these biological functions that has been used for a long time in Chinese medicine and the cosmetics industry in the form of unprocessed plant extracts. Numerous studies have demonstrated that different flavonoid compounds have anti-inflammatory effects in a variety of animal models of inflammation. Particularly, certain flavonoids were discovered to reduce chronic inflammation in numerous animal models used in experiments. Therefore, it may be beneficial to continually assess the anti-inflammatory activity of flavonoids in order to develop a new class of anti-inflammatory drugs as well as anti-inflammatory mechanisms.

Flavones are extensively distributed as glucosides in leaves, flowers, and fruits. Among the main sources of flavones are ginkgo biloba, celery, parsley, red peppers, chamomile, and mint. This group of flavonoids includes the compounds luteolin, apigenin, and tangeritin.

I. **Celery**-Apiumgraveolens L., a member of the apiaceae family, is an annual or perennial plant that thrives in tropical and subtropical parts of Africa, Asia, and all of Europe[60]. About 40 000 tonnes of celery are grown in India each year, and 29 250 tonnes are exported. Celery needs high quantities of moisture for growth but lower temperatures. The best celery may thus be found growing in cold and temperate climates. [61] The seeds, leaves, and essential oils of this plant are among its components that are utilised.[62] One can include carbohydrates, phenols like flavonoids, alkaloids, and steroids as some of the phytochemical components of celery. [63]Celery is the most commonly utilised plant in traditional medicine due to the presence of chemicals including limonene, selinene, frocoumarin glycosides, flavonoids, and vitamins A and C.[64]Celery can prevent rheumatic problems, cardiovascular diseases, jaundice, liver and lien diseases, urinary tract blockage, and gout. Celery leaf ethanol extracts have been shown in studies on rats to boost fertility and promote spermatogenesis. [65-67] Celery lowers blood pressure, blood lipids, and glucose levels, which can help the heart.[68] Celery contains anti-inflammatory and antifungal effects, according to experimental investigations.[69]Its essential oils also have antimicrobial properties. The seeds of this plant can be used to treat tumours, bronchitis, asthenopia, asthma, psoriasis, and other chronic skin conditions. [70]Celery root's diuretic properties make it useful in treatment of colic.

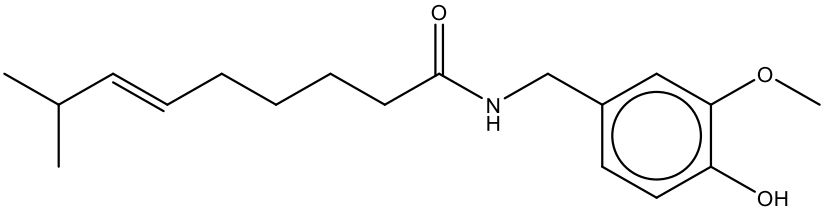
Celery may reduce blood pressure in hypertensive individuals because it has antifungal, anti-inflammatory, and anti-gastric ulcer properties in rats . Celery seed butanol extracts have been shown to reduce lipid peroxidation in diabetic rats by inhibiting oxidative stress . Rats' blood UA levels were

decreased by celery seed and methanol extracts from petroleum. Celery seeds' anti-inflammatory and antioxidant properties, particularly those of their volatile oil and aqueous extracts, haven't been fully studied in relation to gout, though.[71]



LINOLENE

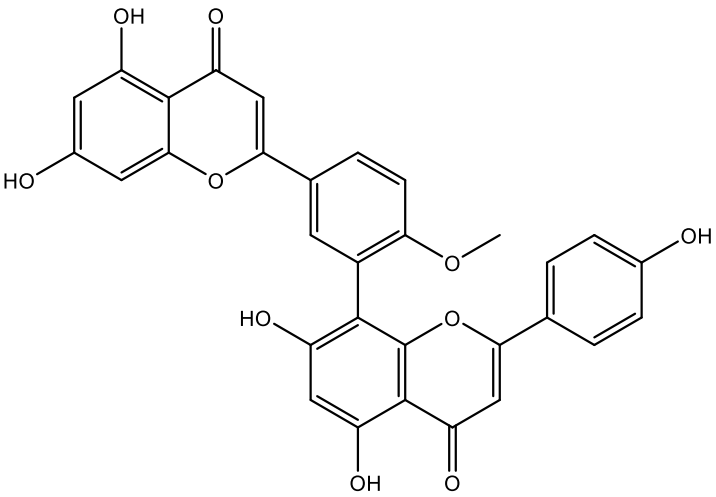
II. **Red Peppers-** For thousands of years, Indian, Native American, African, and Chinese medicinal traditions have employed red peppers as food additives and for a wide range of medical purposes [72,73]. The most eaten species in Brazil is the red pepper Capsicum baccatum L. var. pendulum (Willd.) Eshbaugh (Solanaceae), which is often known as pimentadedo-de-moça and is mostly grown in the South and Southeast[74] Capsaicin has a molecular weight of 305.42 Da and is a derivative of vanillyl amide (8-methyl-N-vanillyl-6-nonenamide). In terms of potency, target, and method of action, capsaicin is known to have two different kinds of effects: a non-selective impact on cells and a short stimulation of primary afferent nerve fibres. Vanilloid receptor 1 (TRPV1), the receptor for capsaicin, has been shown to be abundantly expressed by nociceptive neurons in the trigeminal and dorsal root ganglia[75]. To transmit the feeling of pain, capsaicin binds to the TRPV1 receptor on sensory neurons.In addition to its effects on the nervous system, capsaicin has also been demonstrated to be immunologically active, creating more immune cells as compared to untreated controls.



CAPSAICIN

III. **Ginkgo Biloba -** Ginkgo biloba L. (family: Ginkgoaceae; English name: Maidenhair tree) is a significant source of new herbal medicines with therapeutic effectiveness and various bioactive ingredients. This ancient plant species may reach heights of up to 40 metres, is deciduous, tall, and robust, and has leaves that are fan-shaped and irregularly lobed.[1] In G. Biloba there are 110 known flavonoids, one of which is kaempferol 3-O-l-[6000-p-coumaroyl(d)-glucopyranosyl(1,2)-rhamnopyranoside]. n-BuOH extract of G. biloba leaves included the compounds -7-O-d-glucopyranoside and isorhamnetin 3-O-l-[6000-p-coumaroyl(-d)-glucopyranosyl(1,2)-rhamnopyranoside]. The quercetin 3-O—D-glucopyranoside, quercetin 3-O—rutinoside, kaempferol 3-O—L-[6‴-p-coumaroyl-(-D)-glucopyranosyl-(1,2)-rhamnopyranoside], and quercetin 3-O—L-[6‴-p-coumaroyl-(- 7.O.D. glucopyranoside [26].

GinkgolideA, Amentoflavone , Bilobetin, Ginkgetin, Quercetin, and Bilobalide are the main compound found in Ginkgo Biloba.

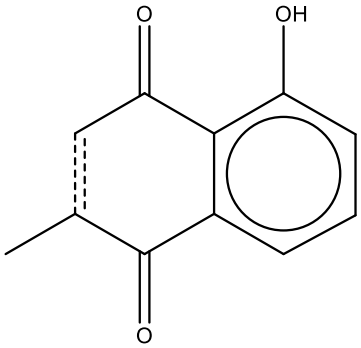


BILOBETIN

3. **Quinones –** Numerous plants, fungi, and mammals all manufacture the quinone chemicals naturally. Some of them were used in medicine as laxatives and in the manufacturing process as colourants. Natural quinone compounds do, however, also have a variety of biological effects, including anti-inflammatory activity . These effects include, but are not limited to, antibacterial, fungicidal, and cytotoxic.

I. Plumbagin

Mostly found in Plumbago species, plumbagin is a naphthoquinone that exhibits a number of pharmacological properties, including anti-inflammatory, neuroprotective, antitumor, and antioxidant actions.Through Nrf2/ARE-mediated regulation of astrogliosis and inhibition of b-secretase enzyme, plumbagin improves cognitive impairments and astrogliosis in STZ-induced mice models of AD.[78] Plumbagin reduced ROS and MDA levels, increased Nrf-2, haemoxygenase 1 and NAD(P)H dehydrogenase quinone 1, and decreased NF-jB, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) levels to suppress Ab25-35-induced oxidative stress. [79] By controlling the expression of NOX4 and downregulating NF-jBsignalling, as well as by inhibiting OGDR-induced NLRP3 inflammasome activation, plumbagin pretreatment might lower ROS generation. [80]

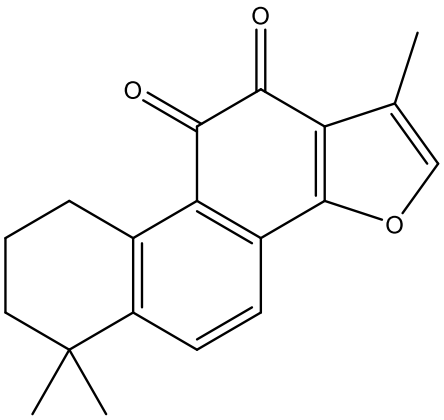


PLUMBAGIN

Tanshinone IIA

Tanshinone IIA possesses anti-inflammatory, antioxidant, and neuroprotective properties and is produced from the dried root or rhizome of Salvia miltiorrhizaeBge[84].[87] In HT22 cells treated with Ab, tanshinone IIA reduced the levels of ROS and MDA, enhanced the activities of SOD and GSH-Px, and lowered the levels of phosphorylate PKR-like (p-PERK), phosphorylate eukaryotic initiation factor 2, and binding immunoglobulin heavy chain protein (Bip)[81] Tanshinone IIA reduced memory loss in Ab1-42-injected mice by reducing the expression of GFAP, COX-2, iNOS,

and NF-kB p65 in a non-genetic animal model of AD. [82] Tanshinone IIA may lower the levels of NLRP3, caspase-1, IL-1b, and IL-18 expression, which can limit the production of proteins and cytokines of the NLRP3 inflammatory signalling pathway in OGD/R BV-2 cells. [83]

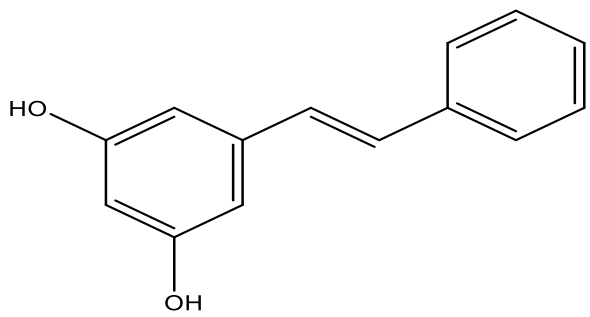


TANSHINONE IIA

STILBENES

Pinosylvin (3,5-dihydroxy-trans-stilbene) is a naturally occurring pre-infectious stilbenoid toxin that is mostly found in the Pinaceae family, especially in the heartwood of Pinus spp. (such as Pinussylvestris) and in pine leaves (Pinusdensiflora). East Asians have long employed various pine tree pieces for a variety of ailments, including the treatment of liver poisoning, stomach issues, and inflammation. Pine needles were frequently used to make tea and meals in South Korea [84]. The Vitaceae family of plants, which includes the well-known wine grape Vitisvinifera L., is among the most prolific sources of newstilbenes currently known. Other groups include Fabaceae, Dipterocarpaceae, and Gnetaceae[85]. A broad variety of plants, notably pines, are thought to use pinosylvin as a defensive mechanism against diseases and insects [86]. They may be found in different kinds of plants, such as mosses and ferns, in addition to most berries and fruits [87]. Under the impact of several biotic and abiotic stressors such wounds, herbivores, fungi, ozone, and UV radiation, pinosylvin produces phytoalexins via reacting malonyl-CoA with cinnamoyl-CoA [88].

Pinosylvin is a natural substance that has potential uses in the creation of antimicrobial food packaging systems because of its intrinsic antibacterial activity, particularly against Campylobacter spp. [89,90]. The growth of Campylobacter jejuni and Campylobacter coli American type culture collection (ATTC) reference strains and clinical isolates has been shown to be inhibited by pinosylvin or its inclusion complexes (ICs) with modified cyclodextrins (hydroxypropyl-b-cyclodextrin and hydroxypropyl-g-cyclodextrin). The MIC range for the pure substance was 25–50 mg/mL, whereas the range for the ICs was 16–64 mg/mL. In addition, time-kill experiments demonstrated that pinosylvin ICs have bactericidal activity against both Campylobacter species at 37 C and even at 4 or 20 C.[91]



PINOSYLVIN

TABLE 1: Plant and their specific chemical compound for inhibition of COX

Serial no.	Class	Plant	Biological Source	Chemical Compound	Family
	Alkaloid				
1		Tree Turmeric /Berberisaristata	Curcuma longa	Berberine	Zingiberaceae
2		Blood Root	Sanguinariacanadensis L	Sanguinarine	Papaveraceae
3		Corydalis	Corydalis impatiens	Cavidine	Papaveraceae
4		Linearis	Isolated from tubers of Corydalis turtschaninovi	Pseudocoptisine	Papaveraceae
	Flavanoids				
5		Celery	Apiumgraveolens L.	limonene, selinene, frocoumarin	Apiaceae
6		Red pepper	Capsicum baccatum L.	Capsaicin	Solanaceae
7		Maidenhair tree	Ginkgo biloba L.	Amentoflavone , Bilobetin, Ginkgetin, Quercetin	Ginkgoaceae
	Quinones				
8		Chitrak	Plumbagozeylanica L	Plumbagin	Plumbaginaceae
9		Red sage or Danshen	Salvia miltiorrhiza Bunge	Tanshinone IIA	Lamiaceae
	Stilbenes				
10		Heartwood of Pinus	PinussylvestrisPinusdensiflora	Pinosylvin	Pinaceae

TABLE 2: Compounds classified on basis of molecular formula, their molecular weight and presence of heavy atom and rotatable bonds

Sr. No.	Compound	Molecular Formula	Molecular Weight (g/mol)	Heavy atoms	Aromatic heavy atoms	Rotatable bonds
1	Berberine	$C_{20}H_{18}NO_4^+$	336.36	25	16	2
2	Sanguinarine	$C_{20}H_{14}NO_4^+$	332.33	25	18	0
3	Cavidine	$C_{21}H_{23}NO_4$	353.41	26	12	2
4	Pseudocoptisine	$C_{19}H_{14}NO_4^+$	320.32	24	16	0
5	Linolene	$C_{10}H_{16}$	136.23	10	0	1
6	Capsaicin	$C_{18}H_{27}NO_3$	305.41	22	6	10
7	Bilobetin	$C_{31}H_{20}O_{10}$	552.48	41	32	4
8	Plumbagin	$C_{11}H_8O_3$	188.18	14	6	0
9	Tanshinone IIA	$C_{19}H_{18}O_3$	294.34	22	11	0
10	Pinosylvin	$C_{14}H_{12}O_2$	212.24	16	12	2

According to Table 2, Bilobetin having highest molecular weight of 552.48 gm/mol and linolene have lowest molecular weight of 136.23 gm/mol. Bilobetin also having highest heavy atom, aromatic heavy atoms among compounds.Capsaicin having highest rotatable bond of 10,

TABLE 3: Lipinski Rule, Drug Likeness, Hydrogen bond acceptor, Hydrogen bond donors and Lipohilicity.

Sr. No.	Compound	LIPINSKI RULE	DRUG LIKENESS	H-bond acceptors	H-bond donors	Lipophilicity(Log p)
		P/F	**Y/N**			
1	Berberine	P	N	4	0	-5.78
2	Sanguinarine	P	N	4	0	-5.17
3	Cavidine	P	N	5	0	-6.01
4	Pseudocoptisine	P	Y	4	0	-5.78
5	Linolene	P	N	0	0	-3.89
6	Capsaicin	P	N	3	2	-5.62
7	Bilobetin	P	N	10	5	-5.86
8	Plumbagin	P	N	3	1	-6.11
9	Tanshinone IIA	P	N	3	0	-5.02
10	Pinosylvin	P	N	2	2	-5.12

According to table 3 all compound follow Lipinski rule of five [molecular mass less than 500 dalton, high lipophilicity(log P value less than 5), less than 5 hydrogen bind doner, less than 10 hydrogen bond acceptor, molar refractive should be between 40-130]. assesses qualitatively the chance for a molecule to become an oral drug with respect to bioavailability. Drug-likeness was established from structural or physicochemical inspections of development compounds advanced enough to be considered oral drug-candidates.

TABLE 4: INSILICO STUDY ADME STUDIES

COMPOUND	WATER SOLUBILITY	GI ABSORPTION	BBB PENETRATION	P GLYCOPROTEIN SUBSTRATE	CYTOCHROME P450 INHIBITOR	BRENK (metabolic stability)	PAINS	LEADLINESS
Berberine	Moderately soluble	High	YES	YES	YES (CYP2D6, CYP3A4, CYP1A2)	UNSTABLE(quaternary nitrogen 1)	0 ALERT	NO
Sanguinarine	Moderately soluble	High	YES	YES	YES (CYP1A2, CYP2C9)	UNSTABLE(polycyclic aromatic hydrocarbon 3, quaternary nitrogen 1)	0 ALERT	NO
Cavidine	Moderately soluble	High	YES	NO	YES(CYP2D6, CYP3A4, CYP2C19)	STABLE	0 ALERT	NO
Pseudocoptisine	Moderately soluble	High	YES	YES	YES(CYP1A2, CYP3A4)	UNSTABLE(quaternary nitrogen 1)	0 ALERT	YES
Linolene	Soluble	Low	YES	NO	YES(CYP2C9)	UNSTABLE(isolated alkene)	0 ALERT	NO
Capsaicin	Soluble	High	YES	NO	YES (CYP1A2, CYP2D6, CYP3A4)	UNSTABLE(isolated alkene)	0 ALERT	NO
Bilobetin	Poorly soluble	Low	NO	NO	YES(CYP2C9)	STABLE	0 ALERT	NO
Plumbagin	Soluble	High	YES	NO	YES(CYP1A2)	STABLE	2 ALERT	NO
Tanshinone IIA	Moderately soluble	High	YES	YES	YES(ALL)	UNSTABLE(diketo group)	2 ALERT	NO
Pinosylvin	Soluble	High	YES	NO	YES(CYP1A2, CYP2C9)	UNSTABLE(stilbene)	0 ALERT	NO

ADME studies of given compound done by the SWISS ADME, according to TABLE 4linolene, capsaicin, plumbagin are solublein water bilobetin is poorly solublein water and rest are moderately soluble. Linolene and Bilobetin have low GI absorbtion, Bilobetindoes not crosses theblood brain barrier.All compound inhibit Cytochrome p450, metabolically stable compound are cavidine, Bilobetin and plumbagin and there is pain alert in two compound i.e. plumbagin and Tanshinone IIA.

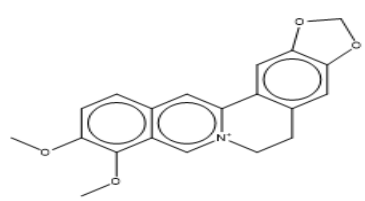
TABLE 5: IN –SILICO TOXICITY PROFILE OF 10 SECONDRY METABOLITES

SR NO.	COMPOUND	LD 50 DOSE	TOXICITY CLASS	CARCINOGENIC	MUTAGENIC	IMMUNOTOXIC	CYTOTOXIC	TOX-21 STRESS RESPONSE PATHWAY	TOX-21 NUCLEAR RECEPTOR SIGNALING PATHWAY
1	Berberine	200 mg/kg	III	ACTIVE	ACTIVE	ACTIVE	ACTIVE	Mitochondrial Membrane Potential (MMP)	Aryl Hydrocarbon Receptor(AhR)
2	Sanguinarine	778mg/kg	IV	ACTIVE	ACTIVE	ACTIVE	INACTIVE	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE) ; Heat shock factor response element (HSE)	Aryl Hydrocarbon Receptor(AhR)
3	Cavidine	940mg/kg	IV	ACTIVE	ACTIVE	ACTIVE	ACTIVE	Mitochondrial Membrane Potential (MMP)	INACTIVE
4	Pseudocoptisine	200mg/kg	III	ACTIVE	ACTIVE	ACTIVE	ACTIVE	Aryl hydrocarbon Receptor (AhR)	INACTIVE
5	Linolene	4400mg/kg	V	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE
6	Capsaicin	47mg/kg	II	ACTIVE	ACTIVE	ACTIVE	INACTIVE	INACTIVE	Aromatase

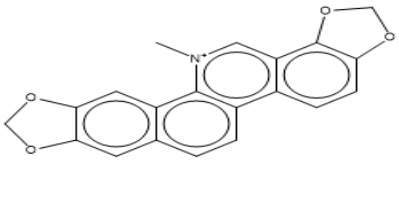
7	Bilobetin	4000mg /kg	V	INACTIV E	INACTIVE	ACTIVE	INACTI VE	Mitochondrial Membrane Potential (MMP) ; ATPase family AAA domain-containing protein 5 (ATAD5)	Estrogen Receptor Alpha (ER)
8	Plumbagin	16mg/k g	II	ACTIVE	ACTIVE	INACTIV E	INACTI VE	Mitochondrial Membrane Potential (MMP) ; ATPase family AAA domain-containing protein 5 (ATAD5)	Aryl hydrocarbon Receptor (AhR)
9	Tanshinone IIA	1230mg /kg	IV	INACTIV E	INACTIVE	INACTIV E	INACTI VE	Mitochondrial Membrane Potential (MMP)	INACTIVE
10	Pinosylvin	1560mg /kg	IV	INACTIV E	INACTIVE	INACTIV E	INACTI VE	Mitochondrial Membrane Potential (MMP) ; ATPase family AAA domain-containing protein 5 (ATAD5)	Androgen Receptor (AR) ; Estrogen Receptor Alpha (ER)

In toxicity studies via software (Protox II) we studied that, Linolene and Bilobetin are the two compound which are belonging to class V drug (may be toxic if swallowed). Linolene completely non toxic but it has value of Ld 50 > 4000, Bilobetin is immunotoxic andalso active in Tox-21 stress response pathway(mitochondrial membrane potential and ATPase family AAA domain containing protein 5) and Tox -21 nuclear receptor signaling pathway(estrogen receptor alpha).

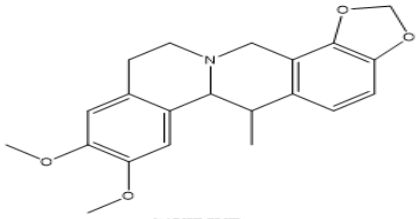
COMPOUNDS AND THEIR STRUCTURES :



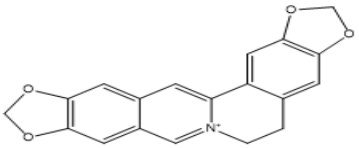
BERBERINE



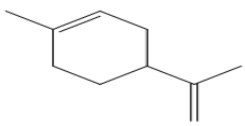
SANGUINARINE



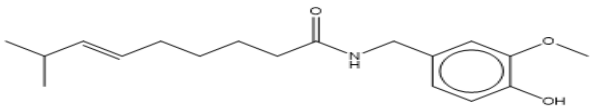
CAVIDINE



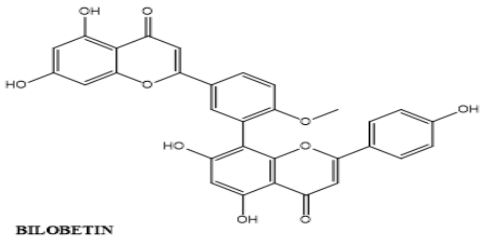
PSEUDOCOPTISINE



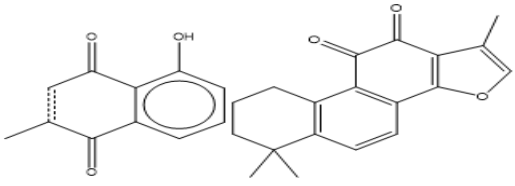
LINOLENE



CAPSAICIN

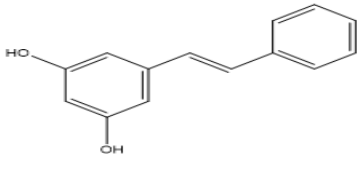


BILOBETIN



PLUMBAGIN

TANSHINONE IIA



PINOSYLVIN

RESULT

Lipinski rule of five [molecular mass less than 500 dalton, high lipophilicity(log P value less than 5), less than 5 hydrogen bind doner, less than 10 hydrogen bond acceptor, molar refractive should be between 40-130]. All compound that we discussed in this article are follow Lipinski rule of five.

Drug likeness are the guidelines for structural properties of compound used for drug like character of a molecule or compound. Only compound 4 (pseudocoptisine) having drug like character.

The drug's lipophilicity, a crucial component of its solubility, absorption, membrane penetration, plasma protein binding, distribution, and tissue penetration, is closely correlated with logP. The Lipinski rule of five includes logP as a part because of the significance of medication lipophilicity. The partition coefficient of a molecule between the aqueous and lipophilic phases—typically octanol and water—is defined as logP. The amount of solute dissolved in each phase is calculated experimentally by dissolving the substance in an immiscible biphasic solution of lipids and water. Drug lipophilicity(Log p) of compound is must be less than 5, all of these compound follow lipophilicity.

Water solubity of compound 5,6,8,and 10 are completely soluble, compound 1,2,3,4,9 are moderately soluble and compound 8 is poorly soluble. Gastrointestinal absortion is low of compound 5 and 7 and rest compound 1,2,3,4,6,8,9,10 compound having high GI absorption. Only compound 7(Bilobetin) does not cross blood brain barrier rest other compound can cross BBB barrier. Compound 1,2,4,9 are only glycoprotein permeable.

Cytochrome p 450 inhibitor, it is the most common mechanism for drug-drug interaction Berberine inhibits CYP2D6, CYP3A4, CYP1A2 inhibitor, Sanguinarineinhibit CYP1A2 and CYP2C9 inhibior, Cavidine inhibits CYP2D6 and CYP3A4 inhibitr, Pseudocoptisine inhibit CYP1A2 and CYP3A4 inhibitor, Linolene only inhibits CYP2C9 inhibitor, Capsaicin inhibit CYP1A2, CYP2D6 and CYP3A4, Bilobetin only inhibits CYP2C9 inhibitor,Plumbaginonly inhibits CYP1A2 inhibitor, Tanshinone IIA inhibits all cytochrome p450 inhibitor, Pinosylvin inhibits CYP1A2 and CYP2C9.

Compound 3,7,8 are completely metabolically stable in among compound, compound 1,4 is unstable because of having quaternary nitrogen1,compound 2 is unstable because of having polycyclic aromatic hydrocarbon and quaternary nitrogen1, compound 5,6 is unstable because of having isolated alkene, compound 9 is unstable because of having diketo group, and compound 10 is stable because of having stillbene. Only compound 8 and 9 shows pain alert rest other have 0 pain alert.

In toxicity study of compound 1-10 via PROTOX II softwere shows compound 5 and 7 are only compound which are belongs to class v drug means these compound can leads to toxic if sollowed. Linolene completely non toxic but it has value of Ld 50 > 4000, Bilobetin is immunotoxic and also active in Tox-21 stress response pathway(mitochondrial membrane potential and ATPase family AAA domain containing protein 5) and Tox -21 nuclear receptor signaling pathway(estrogen receptor alpha).

DESCUSSION

In this article compounds on the basis of their ADME best compound is found to beTanshinone IIA but it is metabolically unstable due to its diketo group and also shows 2 pain alert and on basis of toxicity Tanshinone IIA, Bilobetin are the compound which show least toxicity. In future aspect further research on these compound may show effective results.

Conclusion

A wide range of pharmacological properties are possessed by various active ingredients derived from plant resources. One of the most notable behaviours that plant compounds are seen to display is cyclooxygenase inhibition. The research makes it abundantly obvious that different plant components inhibit the COX-2 enzyme and have a propensity to prevent fatal disorders.Despite the fact that these resources are readily available and have a low level of toxicity, the number of medications produced from plant materials is still quite small. This might be due to unknown action modes or conventional extraction and isolation techniques.Therefore, more extensive research is required immediately in order to create novel therapeutic molecules.Due to their ability to inhibit COX-2, the natural and

synthesised products alkaloids, coumarin, flavonoids, curcuminoids, stilbenes, xanthine, and anthraquinone, among others, have been explored in this text as anti-inflammatory and anticancer drugs. In this reaserch of compound on the basis of ADME best compound is found to be is Tanshinone IIA but it is metabolically unstable due to its diketo group and also shows 2 pain alert and on basis of toxicity Tanshinone IIA, Bilobetin are the compound which show least toxicity. In future aspect further research on these compound may show effective results.

REFERENCES:

1. Chandel P, Rawal RK, Kaur R. Natural products and their derivatives as cyclooxygenase-2 inhibitors. Future Med Chem. 2018 Oct;10(20):2471-2492. doi: 10.4155/fmc-2018-0120. Epub 2018 Oct 16. PMID: 30325206.
2. Emanuela R, Garret AF. Prostaglandins and Inflammation. *Arterioscler. Thromb. Vasc. Biol.* 31(5), 986–1000 (2011).
3. Reddy MVR, Billa VK, Pallela VR *et al.* Design, synthesis, and biological evaluation of 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-indolyl pyrazolines as cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) inhibitors. *Bioorg. Med. Chem.* 16(7), 3907–3916 (2008)
4. Lin JK, Tsai SH, Lin-Shiau SY, Antiinflammatory and antit-mor effects of flavonoids and flavanoids [J]. *Drug Fut*, 2001, **26**(2): 145-152.
5. Metodiewa D, Kochman A, Karolczak S. Evidence for anti-radical and antioxidant properties of four biologically active N, N-diethylaminoethyl ethers of flavanone oximes: a comparison with natural polyphenolic flavonoid (rutin) action [J]. *BiochemMolBiolInt*, 1997, **41**(5): 1067-1075.
6. Havsteen BH. The biochemistry and medical significance of the flavonoids [J]. *Pharm Ther*, 2002, **96**(1): 67-202.
7. Sheng Jia. *Drug screening in vitro* [M]. Beijing, Chemical Industry Press, 2006: 58-76
8. Jiang Q, Ames BN. γ-Tocopherol, but not α-tocopherol, decreases proinflammatory eicosanoids and inflammation damage in rats. FASEB J 2003; 17(8):816–22.
9. Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: structural, cellular, and molecular biology. Annu Rev Biochem 2000; 69(1):145–82.
10. Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. Annu Rev PharmacolToxicol 1998; 38(1):97–120.
11. Watson DJ, Harper SE, Zhao P-L, Quan H, Bolognese JA, Simon TJ. Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch Intern Med 2000; 160(19):2998–3003.
12. Smith CJ, Morrow JD, Roberts LJ, Marnett LJ. Differentiation of monocytoid THP-1 cells with phorbol ester induces expression of prostaglandin endoperoxide synthase-1 (COX-1). BiochemBiophys Res Commun 1993; 192(2):787–93.
13. Everts B, Währborg P, Hedner T. COX-2-specific inhibitors—the emergence of a new class of analgesic and anti-inflammatory drugs. ClinRheumatol 2000; 19(5):331–43.
14. Hinz B, Brune K. Specific COX-2 inhibitors: prospects of therapy with new analgesic and anti-inflammatory substances. Wien KlinWochenschr 1999; 111(3):103–12.
15. Mason RP, Walter MF, Day CA, Jacob RF. A Biological Rationale for the Cardiotoxic Effects of Rofecoxib. In: Harris RE, Bittman R, Dasgupta D, Engelhardt H, Flohe L, Herrmann H, et al. (eds.). Inflammation in the pathogenesis of chronic diseases: the COX-2 controversy, Springer, Netherlands, Dordrecht, The Netherlands, pp 175–90, 2007.
16. Mason RP, Walter MF, McNulty HP, Lockwood SF, Byun J, Day CA, et al. Rofecoxib increases susceptibility of human LDL and membrane lipids to oxidative damage: a mechanism of cardiotoxicity. J CardiovascPharmacol 2006; 47:S7–14
17. Pallavi, H.M.; Al-Ostoot, F.H.; Vivek, H.K. and Khanum, S.A. Design, Docking, synthesis, and characterization of novel N'(2-phenoxyacetyl) nicotinohydrazide and N'(2-phenoxyacetyl) isonicotinohydrazide derivatives as anti-inflammatory and analgesic agents. *J. Mol. Str.* **2021**, *12047*, 131404, https://doi.org/10.1016/j.molstruc.2021.131404.

18. Mukherjee, P.K.; Bahadur, S.; Harwansh, R.K.; Biswas, S. and Banerjee, S. Paradigm shift in natural product research: traditional medicine inspired approaches. *Phytochem. Rev.* **2017**, *16*, 803-826, https://doi.org/10.1007/s11101-016-9489-6.
19. Khanal, P.; Chawla, U.; Praveen, S.; Malik, Z.; Malik, S.; Yusuf, M.; Khan, S.A. and Sharma, M. Study of Naturally-derived Biomolecules as Therapeutics against SARS-CoV-2 Viral Spike Protein. *J. Pharmaceut. Res. Int*. **2021**, *33*, 211-220, https://doi.org/10.9734/jpri/2021/v33i28A31524.
20. Yusuf, M. Natural antimicrobial agents for food biopreservation. In Food Packaging and Preservation Academic Press: US **2018**, 409-438, https://doi.org/10.1016/B978-0-12-811516-9.00012-9.
21. Ringbom, T.; Huss, U.; Stenholm, Å.; Flock, S.; Skattebøl, L.; Perera, P. and Bohlin, L. Cox-2 inhibitory effects of naturally occurring and modified fatty acids. *J. Nat. Prod.* **2001**, *64*, 745-749, https://doi.org/10.1021/np000620d.
22. Magpantay, H.D.; Malaluan, I.N.; Manzano, J.A.H.; Quimque, M.T.; Pueblos, K.R.; Moor, N.; Budde, S.; Bangcaya, P.S.; Lim-Valle, D.; Dahse, H.M. and Khan, A. Antibacterial and COX-2 Inhibitory Tetrahydrobisbenzylisoquinoline Alkaloids from the Philippine Medicinal Plant Phaeanthusophthalmicus. *Plants* **2021**, *10*, 462, https://doi.org/10.3390/plants10030462.
23. Yusuf, M.; Ahmad, A.; Shahid, M.; Khan, M.I.; Khan, S.A.; Manzoor, N. and Mohammad, F. Assessment of colorimetric, antibacterial and antifungal properties of woollen yarn dyed with the extract of the leaves of henna (*Lawsoniainermis*). *J. Clean. Prod.* **2012**, *27*, 42-50, https://doi.org/10.1016/j.jclepro.2012.01.005
24. Scalbert, A.; Manach, C.; Morand, C.; Rémésy, C. Dietary polyphenols and the prevention of diseases. Taylor Fr. **2005**, 45, 287–306.[CrossRef]
25. Spencer, J.P.E.; Abd El Mohsen, M.M.; Minihane, A.M.; Mathers, J.C. Biomarkers of the intake of dietary polyphenols: Strengths, limitations and application in nutrition research. Br. J. Nutr. **2008**, 99, 12–22. [CrossRef]
26. Beckman, C.H. Phenolic-storing cells: Keys to programmed cell death and periderm formation in wilt disease resistance and in general defence responses in plants? Physiol. Mol. Plant Pathol. **2000**, 57, 101–110. [CrossRef]
27. Graf, B.A.; Milbury, P.E.; Blumberg, J.B. Flavonols, Flavones, Flavanones, and Human Health: Epidemiological Evidence. J. Med.Food**2005**, 8, 281–290. [CrossRef]
28. Arts, I.C.W.; Hollman, P.C.H. Polyphenols and disease risk in epidemiologic studies. Am. J. Clin. Nutr. **2005**, 81, 317S–325S.[CrossRef] [PubMed]
29. Chakraborti AK, Garg SK, Kumar R, Motiwala HF, Jadhavar PS. Progress in COX-2 inhibitors: a journey so far. Curr Med Chem. 2010;17:1563–1593.
30. Llorens O, Perez JJ, Palomer A, Mauleon D. Structural basis of the dynamic mechanism of ligand binding to cyclooxygenase. Bioorg Med Chem Lett. 1999;9:2779–2784.
31. Friedman HL. Influence of isosteric replacements upon biological activity. NASNRS. 1951;206:295–358.
32. Lolli ML, Cena C, Medana C, Lazzarato L, Morini G, Coruzzi G, et al. A new class of ibuprofen derivatives with reduced gastrotoxicity. J Med Chem. 2001;44:3463–3468.
33. Prabhakar C, Reddy GB, Reddy CM, Nageshwar D, Devi AS, Babu JM, et al. Process research and structural studies on nabumetone. Org. Proc. Res. Dev. 1999;3:121–125
34. Sun, Y.; Xun, K.; Wang, Y.; Chen, X. A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs. *Anti-Cancer Drugs*, **2009**, *20*(9), 757-769.
35. Ye, M.; Fu, S.; Pi, R.; He, F. Neuropharmacological and pharmacokinetic properties of berberine: a review of recent research. *J. Pharm. Pharmacol.*, **2009**, *61*(7), 831-837.
36. Fukuda, K.; Hibiya, Y.; Mutoh, M.; Koshiji, M.; Akao, S.; Fujiwara, H. Inhibition by berberine of cyclooxygenase-2 transcriptional activity in human colon cancer cells. *J. Ethnopharmacol.*, **1999**, *66*(2), 227-233.
37. Kuo, C.L.; Chi, C.W.; Liu, T.Y. The anti-inflammatory potential of berberine*in vitro* and *in vivo*. *Cancer Lett.*, **2004**, *203*(2), 127-137.

38. Kuo, C.-L.; Chi, C.-W.; Liu, T.-Y. Modulation of apoptosis by berberine through inhibition of cyclooxygenase-2 and Mcl-1 expression in oral cancer cells. *In Vivo*, **2005**, *19*(1), 247-252.
39. Pandey, M.K.; Sung, B.; Kunnumakkara, A.B.; Sethi, G.; Chaturvedi, M.M.; Aggarwal, B.B. Berberine modifies cysteineq 179 I kappa B alpha kinase, suppresses nuclear factor-kappa Bregulatedantiapoptotic gene products, and potentiates apoptosis *Cancer Res.*, **2008**, *68*(13), 5370-5379
40. G. B. Mahady and C. W. W. Beecher, "Quercetin-induced benzophenanthridine alkaloid production in suspension cell cultures of Sanguinariacanadensis," *Planta Medica*, vol. 60, no. 6, pp. 553–557, 1994.
41. C. Vavreˇckov´a, I. Gawlik, and K. M¨uller, "Benzophenanthridine alkaloids of Chelidoniummajus; I. Inhibition of 5- and 12-lipoxygenase by a non-redox mechanism," *PlantaMedica*, vol. 62, no. 5, pp. 397–401, 1996.
42. J. Lenfeld, M. Kroutil, and E. Marsalek, "Antiinflammatory activity of quaternary benzophenanthridine alkaloids from Chelidoniummajus," *Planta Medica*, vol. 43, no. 2, pp. 161–165, 1981.
43. T. K. Beuria, M. K. Santra, and D. Panda, "Sanguinarine blocks cytokinesis in bacteria by inhibiting FtsZ assembly a bundling," *Biochemistry*, vol. 44, no. 50, pp. 16584–16593, 2005.
44. J. H. Jeng, H. L. Wu, B. R. Lin et al., "Antiplatelet effect of sanguinarine is correlated to calcium mobilization, thromboxane and cAMP production," *Atherosclerosis*, vol. 191, no. 2, pp. 250–258, 2007.
45. H. Ahsan, S. Reagan-Shaw, J. Breur, and N. Ahmad, "Sanguinarine induces apoptosis of human pancreatic carcinoma AsPC-1 and BxPC-3 cells via modulations in Bcl-2 family proteins," *Cancer Letters*, vol. 249, no. 2, pp. 198–208, 2007.
46. M. C. Chang, C. P. Chan, Y. J. Wang et al., "Induction of necrosis and apoptosis to KB cancer cells by sanguinarine is associated with reactive oxygen species production and mitochondrial membrane depolarization," *Toxicology and Applied Pharmacology*, vol. 218, no. 2, pp. 143–151, 2007. Sanguinarine-induced apoptosis is associated with an early and severe cellular glutathione depletion," *Cancer Chemotherapy and Pharmacology*, vol. 51, no. 6, pp. 474–482, 2003.
47. A. R. Hussain, N. A. Al-Jomah, A. K. Siraj et al., "Sanguinarine- dependent induction of apoptosis in primary effusion lymphoma cells," *Cancer Research*, vol. 67, no. 8, pp. 3888–3897, 2007.
48. S. Kim, T. J. Lee, J. Leem, S. C. Kyeong, J. W. Park, and K. K. Taeg, "Sanguinarine-induced apoptosis: generation of ROS, down-regulation of Bcl-2, c-FLIP, and synergy with TRAIL," *Journal of Cellular Biochemistry*, vol. 104, no. 3, pp. 895–907, 2008.
49. V. M. Adhami,M.H. Aziz, H.Mukhtar, andN. Ahmad, "Activation of prodeath Bcl-2 family proteins and mitochondrial apoptosis pathway by sanguinarine in immortalized human HaCaT keratinocytes," *Clinical Cancer Research*, vol. 9, no. 8, pp. 3176–3182, 2003.
50. V. M. Adhami, M. H. Aziz, S. R. Reagan-Shaw, M. Nihal, H. Mukhtar, and N. Ahmad, "Sanguinarine causes cell cycle blockade and apoptosis of human prostate carcinoma cells via modulation of cylin kinase inhibitor-cyclin-cyclindependent kinase machinery," *Molecular Cancer Therapeutics*, vol. 3, no. 8, pp. 933–940, 2004.
51. P. Weerasinghe, S. Hallock, S. C. Tang, B. Trump, and A. Liepins, "Sanguinarine overcomes P-glycoprotein-mediated multidrug-resistance via induction of apoptosis and oncosis in CEM-VLB 1000 cells," *Experimental and Toxicologic Pathology*, vol. 58, no. 1, pp. 21–30, 2006.
52. I. De Stefano, G. Raspaglio, G. F. Zannoni et al., "Antiproliferative and antiangiogenic effects of the benzophenanthridine alkaloid sanguinarine in melanoma," *Biochemical Pharmacology*, vol. 78, no. 11, pp. 1374–1381, 2009.
53. Y. H. Choi, W. Y. Choi, S. H. Hong et al., "Anti-invasive activity of sanguinarine through modulation of tight junctions and matrix metalloproteinase activities in MDAMB- 231 human breast carcinoma cells," *Chemico-Biological Interactions*, vol. 179, no. 2-3, pp. 185–191, 2009.
54. J. Huh, A. Liepins, J. Zielonka, C. Andrekopoulos, B. Kalyanaraman, and A. Sorokin, "Cyclooxygenase 2 rescues LNCaP prostate cancer cells fromsanguinarine-induced apoptosis by

a mechanism involving inhibition of nitric oxide synthase activity," *Cancer Research*, vol. 66, no. 7, pp. 3726–3736, 2006.
55. H. Ahsan, S. Reagan-Shaw, D. M. Eggert et al., "Protective effect of sanguinarine on ultraviolet B-mediated damages in SKH-1 hairless mouse skin: implications for prevention of skin cancer," *Photochemistry and Photobiology*, vol. 83, no. 4, pp. 986–993, 2007.
56. Q. Lu, S. Lu, X.H. Gao, Y.B. Luo, B. Tong, Z.F. Wei, T. Lu, Y.F. Xia, G.X. Chou, Z.T. Wang, Y. Dai, Norisoboldine, an alkaloid compound isolated from Radix Linderae, inhibits synovial angiogenesis in adjuvant-induced arthritis rats by moderating Notch1 pathway-related endothelial tip cell phenotype, Exp. Biol. Med. 237 (2012) 919e932
57. Y. Luo, M. Liu, Y. Xia, Y. Dai, G. Chou, Z. Wang, Therapeutic effect of norisoboldine, an alkaloid isolated from Radix Linderae, on collagen-induced arthritis in mice, Phytomedicine 17 (2010) 726e731.
58. M. Ozawa, S. Kawamata, T. Etoh, M. Hayashi, K. Komiyama, A. Kishida, C. Kuroda, A. Ohsaki, Structures of new Erythrinan alkaloids and nitric oxide production inhibitors from Erythrina crista-galli, Chem. Pharm. Bull. 58 (2010) 1119e1122.
59. Niu, X.; Zhang, H.; Li, W.; Mu, Q.; Yao, H.; Wang, Y. Antiinflammatory effects of cavidine*in vitro* and *in vivo*, a selective COX-2 inhibitor in LPS-induced peritoneal macrophages of mouse. *Inflammation*, **2015**, *38*(2), 923-933.
60. Gauri M, Javed Ali S, Shahid Khan M. A review of Apiumgraveolens (Karafs) with special reference to Unani medicine. Int Arch Integr Med. 2015;2:131-136
61. Kolarovic J, Popovic M, Mikov M, Mitic R, Gvozdenovic L. Protective effects of celery juice in treatments with doxorubicin. Molecules. 2009;14:1627-1638.
62. Bhattacharjee SK. Handbook of Medicinal Plants. 4th ed. Jaipur, India: Pointer; 2004.
63. Khare CP. Indian Medicinal Plants. London, England: Springer Science; 2008.
64. Kooti W, Ali-Akbari S, Asadi-Samani M, Ghadery H, Ashtary- Larky D. A review on medicinal plant of Apiumgraveolens. Adv Herb Med. 2014;1:48-59.
65. Grzanna R, Lindmark L, Frondoza C. Ginger—an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005;8:125-132.
66. ZareMarzouni H, Daraei N, Sharafi-Ahvazi N, Kalani N, Kooti W. The effects of aqueous extract of celery leaves (Apiumgraveolens) on fertility in female rats. World J Pharm Pharm Sci. 2016; 5:1710-1714.
67. Kooti W, Mansori E, Ghasemiboroon M, Harizi M, Amirzarga A. Protective effects of celery (Apiumgraveolens) on testis and cauda epididymal spermatozoa in rat. Iranian J Reprod Med. 2014;12:365-366.
68. Lans CA. Ethnomedicines used in Trinidad and Tobago for urinary problems and diabetes mellitus. J EthnobiolEthnomed. 2006;2:45.
69. Mencherini T, Cau A, Bianco G, Della Loggia R, Aquino RP, Autore G. An extract of Apiumgraveolens var. dulce leaves: structure of the major constituent, apiin, and its anti-inflammatory properties. J Pharm Pharmacol. 2007;59:891-897.
70. Kritikar KR, Basu BD. Indian Medicinal Plants. 2nd ed. Vols and 2. Dehradun, India: International Book Distributors; 2008.
71. Li S, Li L, Yan H, Jiang X, Hu W, Han N, Wang D. Anti-gouty arthritis and anti-hyperuricemia properties of celery seed extracts in rodent models. Mol Med Rep. 2019 Nov;20(5):4623-4633. doi: 10.3892/mmr.2019.10708. Epub 2019 Sep 26. PMID: 31702020; PMCID: PMC6797962.
72. Govindarajan, V. S., Sathyanarayana, M. N. (1991) Capsicum—production, technology, chemistry, and quality. Part V. Impact on physiology, pharmacology, nutrition, and metabolism; structure, pungency, pain, and desensitization sequences. Crit. Rev. Food Sci. Nutr. 29: 435–47
73. Szallasi, A., Blumberg, P. M. (1999) Vanilloid (capsaicin) receptors and mechanisms. Pharmacol. Rev. 51: 159–212
74. Linguanotto, N. (2004) Dicionáriogastronômico: pimentas com suasreceitas. Gaia, Brazil, p. 164

75. Caterina, M. J., Leffler, A., Malmberg, A. B., Martin, W. J., Trafton, J., Petersen-Zeitz, K. R., Koltzenburg, M., Basbaum, A. I., Julius, D. (2000) Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288: 306–313
76. AacuteRbara L. F. B., Michele C. M., Guilherme B. L. d, F. Ginkgo bilobaL.: phytochemical components and antioxidant activity. *African Journal of Pharmacy and Pharmacology* . 2015;9doi: 10.5897/ajpp2015.4373. [CrossRef] [Google Scholar]
77. Hasler A., Gross G.-A., Meier B., Sticher O. Complex flavonol glycosides from the leaves of Ginkgo biloba. *Phytochemistry* . 1992;31(4):1391–1394. doi: 10.1016/0031-9422(92)80298-s. [PubMed] [CrossRef] [Google Scholar]
78. Nakhate KT et al. Plumbagin ameliorates memory dysfunction in streptozotocin induced Alzheimer's disease via activation of Nrf2/ARE pathway and inhibition of b-secretase. Biomed Pharmacother 2018; 101: 379–390.
79. Wang S et al. Plumbagin inhibits amyloid-b-induced neurotoxicity: regulation of oxidative stress and nuclear factor erythroid 2-related factor 2 activation. NeuroReport 2018; 29: 1269–1274.
80. Zhang Q et al. Plumbagin attenuated oxygen-glucose deprivation/reoxygenation- induced injury in human SH-SY5Y cells by inhibiting NOX4-derived ROS-activated NLRP3 inflammasome. BiosciBiotechnolBiochem 2020; 84: 134–142.
81. Liu XQ et al. Sodium tanshinone IIA sulfonate protects against Ab1-42-induced cellular toxicity by modulating Ab-degrading enzymes in HT22 cells. Int J BiolMacromol 2020; 151: 47– 55. pii: S0141-8130(19)39759-4.
82. Maione F et al. Down regulation of pro-inflammatory pathways by tanshinone IIA and cryptotanshinone in a non-genetic mouse model of Alzheimer's disease. Pharmacol Res 2018; 129: 482–490.
83. Cai L et al. The protective effect of tanshinoneiia on oxygen-glucose deprivation and reperfusion injury of microgliathrough the NLRP3 inflammatory signaling pathway. SichuanDaXueXueBao Yi Xue Ban 2016; 47: 660–664.
84. Jeong, E.; Lee, H.-R.; Pyee, J.; Park, H. Pinosylvin Induces Cell Survival, Migration and Anti-Adhesiveness of Endothelial Cells via Nitric Oxide Production: Pinosylvin is a vasoregulating compound. Phytother. Res. **2013**, 27, 610–617. [CrossRef]
85. Riviere, C.; Pawlus, A.D.; Merillon, J.-M. Natural Stilbenoids: Distribution in the Plant Kingdom and Chemotaxonomic Interest in Vitaceae. Nat. Prod. Rep. **2012**, 29, 1317–1333. [CrossRef] [PubMed]
86. Castelli, G.; Bruno, F.; Vitale, F.; Roberti, M.; Colomba, C.; Giacomini, E.; Guidotti, L.; Cascio, A.; Tolomeo, M. In Vitro Antileishmanial Activity of Trans-Stilbene and Terphenyl Compounds. Exp. Parasitol. **2016**, 166, 1–9. [CrossRef] [PubMed]
87. Akinwumi, B.C.; Bordun, K.-A.M.; Anderson, H.D. Biological Activities of Stilbenoids. Int. J. Mol. Sci. **2018**, 19, 792. [CrossRef][PubMed]
88. Park, E.-J.; Park, H.J.; Chung, H.-J.; Shin, Y.; Min, H.-Y.; Hong, J.-Y.; Kang, Y.-J.; Ahn, Y.-H.; Pyee, J.-H.; Kook Lee, S. Antimetastatic Activity of Pinosylvin, a Natural Stilbenoid, Is Associated with the Suppression of Matrix Metalloproteinases. J. Nutr. Biochem. **2012**, 23, 946–952. [CrossRef]
89. Plumed-Ferrer, C.; Väkeväinen, K.; Komulainen, H.; Rautiainen, M.; Smeds, A.; Raitanen, J.-E.; Eklund, P.;Willför, S.; Alakomi, H.-L.; Saarela, M. The Antimicrobial Effects of Wood-Associated Polyphenols on Food Pathogens and Spoilage Organisms. Int. J. Food Microbiol. **2013**, 164, 99–107. [CrossRef]
90. Silva, F.; Domingues, F.C.; Nerín, C. Control Microbial Growth on Fresh Chicken Meat Using Pinosylvin Inclusion Complexes Based Packaging Absorbent Pads. LWT **2018**, 89, 148–154. [CrossRef]
91. Bakrim, S.; Machate, H.;6 Benali, T.; Sahib, N.; Jaouadi, I.; Omari, N.E.; Aboulaghras, S.; Bangar, S.P.; Lorenzo, J.M.; Zengin, G.; et al. Natural Sources and Pharmacological Properties of Pinosylvin. Plants **2022**, 11, 1541. https://doi.org/10.3390/plants1112154.